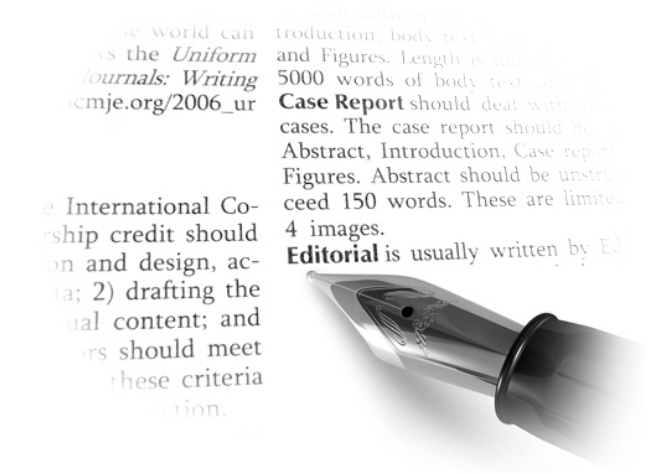

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Editorial

The next step for Burkitt lymphoma

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The successes in the treatment of childhood acute lymphoblastic leukemia (ALL) are well known, with a cure rate of more than 80% of patients treated. However, for the minority of patients who fail to achieve long-term remission, treatment options are limited with overall poor prognosis. Much the same can be said for Burkitt lymphoma today, once considered in the same disease category as precursor B ALL and erroneously treated in a similar manner.

The major characteristics of Burkitt lymphoma are well established; morphologically, Burkitt lymphoma consists of a homogenous population of medium-sized cells with a high mitotic rate [1]. Immunophenotype spectrum includes expression of surface IgM, CD19, CD20, CD22, CD10, CD79a, and negative results for TdT [2]. Above all, important corroborating evidence for the diagnosis of Burkitt lymphoma includes translocations involving the *MYC* gene at locus 8q24. These *MYC* translocations consist of t(8;14)(q24;q32), by far the most common, and t(8;22)(q24;q11) and t(2;8)(p12;p24) to a much lesser extent, all of which result in the realignment of the *MYC* oncogene with immunoglobulin promoter/enhancer elements. Tumor lysis syndrome is an important complication that requires meticulous attention during the early phases of treatment. All of these traits also apply to ALL, L3 and the two entities are now considered to represent different aspects of the same disease.

In the early 1980's, it became known that short, intensive treatment of childhood Burkitt lymphoma, rather than a protracted treatment course, as is commonly administered to patients with precursor B ALL, is highly effective [3]. Under this tenet, multi-center studies including the LMB and BFM studies have contributed significantly to improve the outcome of children with Burkitt lymphoma. Relying on agents such as cyclophosphamide, methotrexate, and cytarabine, and central nervous system (CNS)-directed therapy, these studies have been crucial in elevating the previously dismal survival of the patients to 80% to 90% range. Initial successes in the pediatric population have also had a positive influence on the treatment of adults with Burkitt lymphoma, resulting in major advances in outcome for these patients as well.

In this issue of the Korean Journal of Hematology, Park et al. report the outcomes of children with Burkitt lymphoma/leukemia treated within a single institution in Korea in a long period spanning from 1991 to 2007 [4]. Major conclusions from their study include observations on improved survival of patients treated with the LMB96 protocol in a later cohort of patients when compared to that of a historical cohort who were given D-COMP or CCG-106B protocol treatment. They also underscore that, despite improvements in outcome, CNS disease, high lactate dehydrogenase (LDH) levels at diagnosis, and poor initial treatment response remain adverse prognostic factors.

Overall, their results mirror the progress that has been made in the treatment of Burkitt lymphoma throughout the decades, and, although from a single institution, may encapsulate and exemplify the treatment experience of Burkitt lymphoma. Intensive treatment of short duration indeed resulted in better outcomes for this disease. As in the LMB89 study, elevated LDH, poor response to initial treatment, such as the prephase of COP (cyclophosphamide, vincristine, prednisone), and CNS involvement were adverse prognostic factors [5]. However, the study by Park et al. parallels other major studies on Burkitt lymphoma in that the current shortcomings in diagnosis and treatment of this disease also become evident. The paper, while reflecting the successes of the past, emphasizes the unanswered questions of the disease that remain the tasks of the future.

Despite major leaps in the treatment of Burkitt lymphoma,

for the minority of patients who either relapse or are unresponsive to primary treatment, valid options are limited and the prognosis is poor. For pediatric hematologists and oncologists living today, it is these children who warrant our attention and who may be better served by both better diagnosis and treatment.

With regards to diagnosis, cytogenetic studies are fundamental. It is interesting to note that even in the past LMB89 study, cytogenetic data was only available in 175 out of 561 patients eligible for analysis. However, such data, which have now become a basic component of initial diagnosis, are important not only for diagnostic verification, but also possibly as a mean of risk stratification. With the subsequent FAB/LMB 96 study reporting on the inferior outcomes of patients with +7q or del(13q) [6], results of cytogenetic studies may aid in predicting overall prognosis of the patient, and in dictating therapy.

The 2008 WHO classification lists a disease entity known as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma (DLBCL) and Burkitt lymphoma, evidence of the often indistinguishable barrier between these two disease states [7]. Future diagnostics should attempt to clarify diseases boundaries as much as possible, and studies on global gene expression profiling may aid in the accurate diagnosis of patients when morphological and immunohistochemical data give conflicting or inconclusive results. Inaccurate initial diagnosis and therapy may result in subsequent resistance to treatment in this rapidly cycling tumor, with life-threatening consequences.

Innovative therapeutic trials are also necessary. Use of monoclonal antibodies such as rituximab (anti-CD20 antibody) and epratuzumab (anti-CD22 antibody) for the treatment of mature lymphoma has shown promising results in adult patient-based trials, and requires verification in children. A greater understanding of the role of MYC protein in both tumorigenesis and apoptosis may open a window into the use of novel therapeutic drugs [8].

So the next steps in the diagnosis and treatment of Burkitt lymphoma are daunting but necessary tasks: greater diagnostic clarity and possible risk stratification through both cytogenetic and molecular methods, and the implementation of new therapeutics in those who fail to respond to current strategies. Recent studies on patients with Burkitt lymphoma, as found in this issue, both validate the successes of the past and, above all, remind us of our current limitations.

REFERENCES

1. de Leval L, Hasserjian RP. Diffuse large B-cell lymphomas and burkitt lymphoma. Hematol Oncol Clin North Am 2009;23:791-827.
2. Kenkre VP, Stock W. Burkitt lymphoma/leukemia: improving prognosis. Clin Lymphoma Myeloma 2009;9(Suppl 3):S231-8.
3. Patte C. Treatment of mature B-ALL and high grade B-NHL in children. Best Pract Res Clin Haematol 2002;15:695-711.
4. Park ES, Kim H, Lee JW, et al. Treatment outcomes in children with burkitt lymphoma and L3 acute lymphoblastic leukemia treated using the lymphoma malignancy B protocol at a single institution. Korean J Hematol 2011;46:96-102.
5. Patte C, Auperin A, Michon J, et al. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370-9.
6. Poirel HA, Cairo MS, Heerema NA, et al. Specific cytogenetic abnormalities are associated with a significantly inferior outcome in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. Leukemia 2009;23:323-31.
7. Swerdlow SH, Campo E, Harris NL, et al, eds. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2008.
8. Klapproth K, Wirth T. Advances in the understanding of MYC-induced lymphomagenesis. Br J Haematol 2010;149:484-97.